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# Early human brain development: Starring the subplate

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## ABSTRACT

This review summarizes early human brain development on the basis of neuroanatomical data and functional connectomics. It indicates that the most significant changes in the brain occur during the second half of gestation and the first three months post-term, in particular in the cortical subplate and cerebellum. As the transient subplate pairs a high rate of intricate developmental changes and interactions with clear functional activity, two phases of development are distinguished: a) the transient cortical subplate phase, ending at 3 months post-term when the permanent circuitries in the primary motor, somatosensory and visual cortices have replaced the subplate; and subsequently, b) the phase in which the permanent circuitries dominate. In the association areas the subplate dissolves in the remainder of the first postnatal year. During both phases developmental changes are paralleled by continuous reconfigurations in network activity. The reviewed literature also suggests that disruption of subplate development may play a pivotal role in developmental disorders, such as cerebral palsy, autism spectrum disorders, attention deficit hyperactivity disorder and schizophrenia.

## 1. Introduction

The brain is a magnificent organ allowing its owner to interact with other beings and objects, to flexibly adapt to ever changing situations, to predict and – in human beings – to reflect. One may wonder, how does the brain with its about 85 billion neurons and its trillions of connections and synapses accomplish this multifaceted, miraculous task (Azevedo et al., 2009; estimated numbers in the human brain)?

The aim of the present article is to review current knowledge on early human brain development. Focus is on the first phases of development, i.e., the prenatal period and the first two years of postnatal life. Special attention is paid to the transiently present cortical subplate and its critical role in early brain development. The body of the paper starts with a short overview of adult brain function in order to understand the ‘end stage’ of development (section 2). I consider the age period of 20 to 50 years as being representative of the adult stage of brain development, in accordance with the ages of the subjects in the majority of studies on the adult human brain. However, it should be realized that the human brain changes continuously over the life span, with developmental processes occurring until the age of 40 years (see section 3) and processes of ageing, including a decline of white matter integrity, starting around the age of 50 years (Bender et al., 2016; Barrick et al., 2010). The section on adult brain function includes information on functional connectivity, as functional connectomics will be incorporated in the description of the developing brain. The third section contains the body of the paper, i.e., the review of early human brain

development. It reviews knowledge on structural brain development, using human data when available, and ties this information with current knowledge on functional connectomics during early human brain development. The combination of the two literature sources highlights that the most significant changes in the brain occur during the second half of gestation and the first three months post-term, in particular in the cortical subplate and cerebellum. As the transient subplate pairs a high rate of complex developmental changes and interactions with clear functional activity, two phases of development are distinguished: a) the transient cortical subplate phase, primarily present from early fetal life to 3 months post-term; and subsequently, b) the phase in which the permanent circuitries dominate (see Kostović et al., 2014a, 2014b). The reviewed literature suggests that disruption of subplate development may play a pivotal role in developmental disorders, such as cerebral palsy, autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD) and schizophrenia. The two phases in brain development largely correspond to those observed in motor behavior: in the first phase varied motor behavior mainly serves exploration and much less adaptation to the environment, whereas in the second phase developing motor behavior can be adapted with increasing efficiency to environmental constraints (Hadders-Algra, 2018a). It allows the infant to learn to reach and grasp, to sit, stand and walk and to chew and talk.

The review zooms in on material relevant to the paper’s focus; this implies that the review is not an exhaustive examination of all developmental processes in early human brain development.

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## 2. Adult brain function

### 2.1. Evolution of the human brain

The wealth of human behavior is attributed to the cerebral cortex, the part of the brain that expanded greatly during evolution (Krubitzer and Kaas, 2005; Rakic, 2009). For instance, in insectivores such as the hedgehog, the cerebral cortex occupies 10%–20% of total brain volume, whereas in the human this proportion has risen to about 80% (Frahm et al., 1982; Hofman, 2014). The enlargement of the cerebral cortex has not so much been brought about by an increase in cortical thickness; its increase is especially due to an expansion of the surface area (Mota and Herculano-Houzel, 2015; Rakic, 2009). This expansion is associated with an increase in size, number and complexity of the cortex' vertical modules (Geschwind and Rakic, 2013). It allowed for the emergence of new areas such as language related areas and the extension of the prefrontal cortex and association areas (Hofman, 2014). Interestingly, the volume of the white matter - mostly consisting of cortico-cortical connections - increased more during the evolutionary expansion of the cortex than the volume of gray matter (Frahm et al., 1982; Hofman, 2014; Zhang and Sejnowski, 2000). In addition, motor control got increasingly corticalized, i.e., during primate evolution the number of cortical motor neurons increased substantially more than the neurons in the spinal cord. For instance, in relatively small primates the ratio between cortical motor neurons and spinal neurons is about 2:1, whereas it is about 20:1 in the human (Herculano-Houzel et al., 2016). The impact of this corticalization is illustrated by the so-called locked-in syndrome. This human syndrome, that is characterized by mutism and quadriplegia, is caused by a bilateral complete lesion of the corticospinal tract in the lower brain or brainstem. In small and medium-sized primates such lesion causes only a loss of fine motor control in the upper limbs, whereas motor control of the rest of the body is intact (Herculano-Houzel et al., 2016).

### 2.2. Spontaneous activity, functional connectivity and reuse

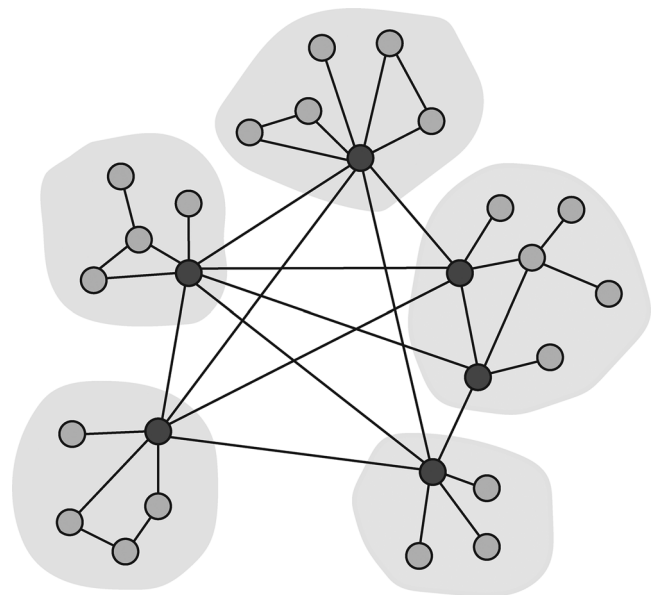
Concepts on human brain function largely changed during the last century. The earlier view that the brain primarily is a reactive organ organised in chains of reflexes was replaced by the notion that spontaneous, intrinsic activity is the brain's major function (Raichle, 2015; Sherrington, 1906). Indeed, animal and human studies showed that spontaneous, patterned activity is a prominent property of cortical networks at any age and at any cerebral location (Blankenship and Feller, 2010; Katz and Shatz, 1996; Khazipov et al., 2004; Penn and Shatz, 1999; Raichle, 2015). This activity is even present in the cortex of anaesthetized adult macaque monkeys, even at anaesthetic levels that induce profound levels of unconsciousness. This implies that the activity is also present in the absence of typical perception or behaviour (Vincent et al., 2007). The spontaneous patterned activity is a property that is brought about by heterogeneous mechanisms, such as pacemaker-like neurons, extrasynaptic glutamate and gap junctions (Blankenship and Feller, 2010). The redundancy in mechanisms provides the brain with resilience: when one element in the circuitry of a network is disrupted, other mechanisms will substitute function so that spontaneous activity can persist (Blankenship and Feller, 2010).

Due to the expanding capacities of functional magnetic resonance imaging (fMRI), knowledge on adult human brain function in vivo has rapidly increased. One of the techniques is resting state fMRI, that measures the level of spatiotemporal correlation between brain signals during rest. Resting state fMRI studies in adult persons indicated that the brain's spontaneous activity is spatially organized in endogenous low-frequency oscillations that vary over time (Broyd et al., 2009; Raichle, 2015). At least eight resting state networks have been distinguished, including a primary motor, a primary visual, an attentional and a so-called default-mode network. The latter network plays a role in internally focused tasks such as episodic memory, self-referential

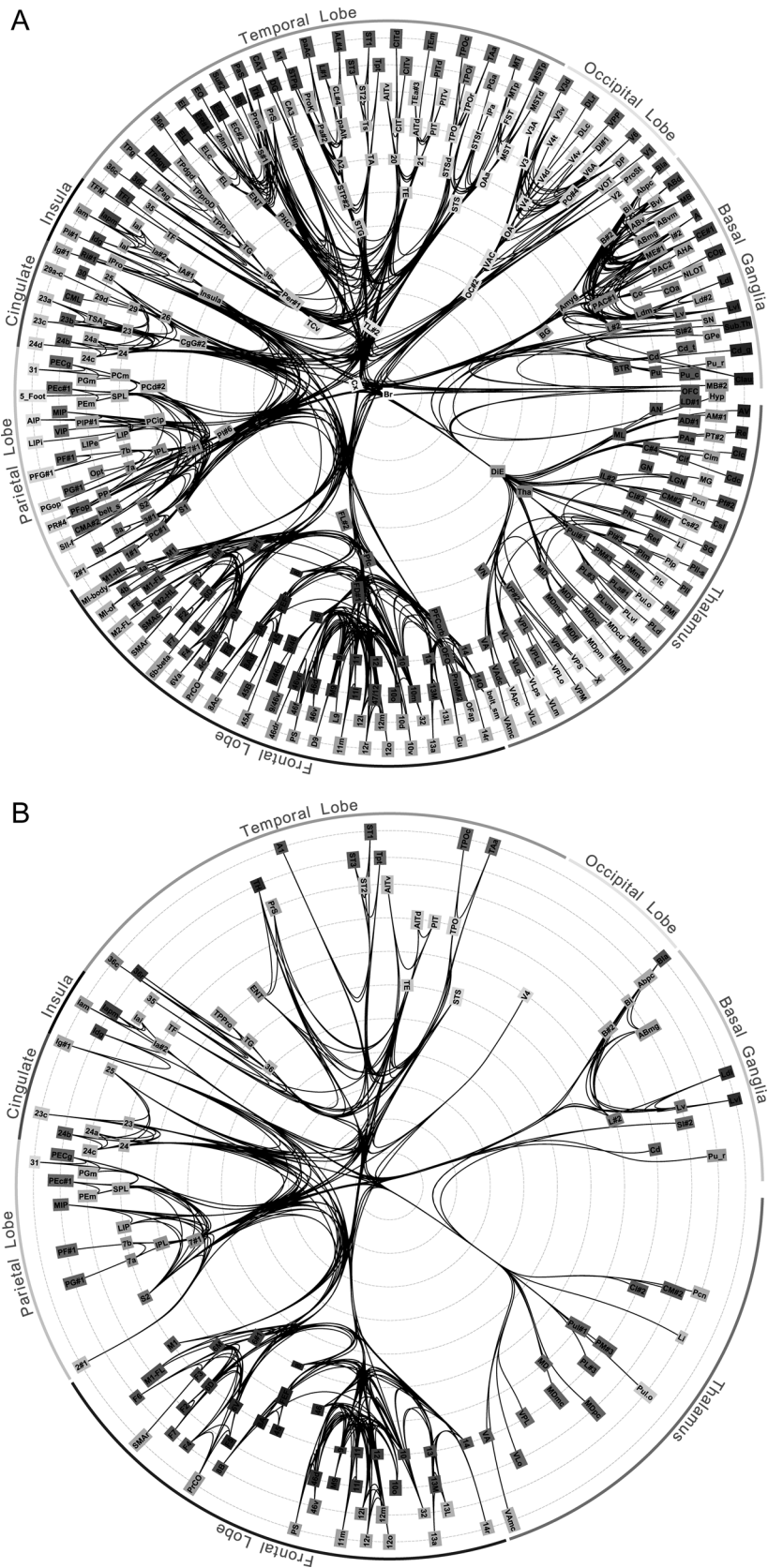
thought and other social cognitive processes (Raichle, 2015; Van den Heuvel and Hulshoff Pol, 2010). The activity in the default-mode network increases during rest, whereas in the other networks activity increases during tasks (Raichle, 2015; Van den Heuvel and Hulshoff Pol, 2010).

What could be the function of the continuously present spontaneous activity in the brain? This question is even more pressing when we realize the high energy costs of this activity: in the human adult, brain weight represents about 2% of body weight, but the brain uses about 20% of energy consumption. The energy is especially used for neuronal activity and not for brain maintenance activities such as neuronal repair (Raichle and Mintun, 2006). On the basis of accumulating evidence on the function of the brain's spontaneous activity (e.g., Bar, 2007; Hartmann et al., 2015; Luczak et al., 2013; Zhang et al., 2008) Raichle hypothesized that the brain's intrinsic spontaneous activity assists the organisation of incoming information, data interpretation, response generation, and preparation of the brain for upcoming events (Raichle, 2015).

The fMRI data gave rise to functional connectomics. The data showed that the human brain - as other highly complex social and biological systems - uses a combination of local and global network organisation, an organization allowing for maximal complexity and interplay, therewith creating the basis for behavioural adaptability (Sporns et al., 2002). However, the global organisation calls for long-range connections that carry specific biological costs, as the efficient transport of a neural signal over long distances requires thick and/or myelinated axons that are expensive in terms of energy and space (Bullmore and Sporns, 2012; Van den Heuvel et al., 2016). To cope with the limits imposed by the biological costs, the human brain applies a dual organisational approach: it combines the global network organisation with a very efficient local network organisation (Bullmore and Sporns, 2012). The local networks (or - in a social analogy - 'communities'), consist of multiple 'nodes', i.e., neurons or groups of neurons (in the analogy 'families'; see Fig. 1). The local networks have a so-



**Fig. 1.** Schematic representation of global and local network organisation. The grey zones represent the local networks ('communities') with small-world architecture characterised by short path length and clustering. The circles depict the nodes, i.e., the neurons or groups of neurons ('families') within the local community. The dark grey nodes represent the hubs that communicate via long distance connections with other communities. In network organisation terminology the configuration of the hubs is known as the 'rich club'. It represents the high-cost, high-capacity backbone assumed to enable efficient network communication. (Van den Heuvel et al., 2016).



**Fig. 2.** Global impression of the whole brain connectivity structure, based on the neuroinformatic database of the macaque brain. A) Long distance connectivity in the cortex and subcortex; B) The innermost ‘core’ circuit that is far more tightly integrated than the overall network. The ‘core’ circuit consists of the brain areas with high connectivity between nodes (‘hubs’ – areas with many connections); the cortical hubs are especially located in the (superior) frontal and parietal areas. Note that the label basal ganglia refers here to the ‘basal brain ganglia’, i.e., the nuclei at the base of the forebrain, including the amygdala. For details, see the original figure, i.e., [Figs. 1 and 3 of Modha and Singh, 2010](#). Figure reproduced from this publication with permission from the authors and Proceedings of the National Academy of Sciences of the United States of America.

called ‘small-world’ architecture (‘the bonds between families’), i.e., they are characterised by strong local connectivity with a short average path length between the neurons with a high local clustering and relatively few long range connections ([Park and Friston, 2013](#); [Stam,](#)

[2014](#); [Watts and Strogatz, 1998](#)). A study evaluating the network cost-efficiency of the ‘small-world’ architecture during resting state fMRI in monozygotic and dizygotic same sex twins indicated that the ‘small world’ architecture has a high heritability ([Fornito et al., 2011](#)). The



high heritability of the brain's network efficiency, i.e., the ability to find the optimal balance between global and local connectivity, may explain why genetics also have a large impact on intelligence (Deary et al., 2010).

Within the local networks certain nodes function as hubs, i.e., they are the centres on which the global long-range connectivity converges. Important hubs have been localised in the cortical precuneus, superior frontal and superior parietal cortex, and the subcortical hippocampus, thalamus, putamen and amygdala (Park and Friston, 2013; Pessoa, 2014). These important hubs form a core circuit, that has a strong internal connectivity and a vast connectivity with the rest of the brain (see Fig. 2; Modha and Singh, 2010; Pessoa, 2014). In daily life, activity in the functional cortico-cortical, cortico-subcortical and subcortical-subcortical networks is continuously reconfigured (Cocchi et al., 2013; Cole et al., 2013; Kipping et al., 2013; Pessoa, 2014). In fact it is increasingly recognized that a particular node or connection may be engaged in multiple cognitive and behavioural contexts (Mišić and Sporns, 2016). This means, that although brain areas and networks have a genetically determined preference for specialization in specific tasks (Sun et al., 2005; Yang et al., 2016), local networks also are used – and thus reused – in many different tasks (Anderson, 2014, 2016a, 2016b; Anderson and Penner-Wilger, 2013; Pessoa, 2014).

In short, the adult brain is characterized by spontaneous activity in local and global networks that are continuously involved in changing coalitions, in which a specific coalition depends on the specifics of the task and context. This also means that neural behaviour is characterized by degeneracy, i.e., the ability of structurally different elements (e.g., different coalitions) to perform the same function (Edelman and Gally, 2001). In other words, the brain is characterized by continuous spontaneous activity allowing its owner to vary and adapt behaviour – for the brain many roads lead to Rome (Abe and Sternad, 2013; Bar, 2007; Hadders-Algra, 2018a; Van der Fits et al., 1998).

### 3. Early human brain development

#### 3.1. The transient subplate phase

##### 3.1.1. Structural development

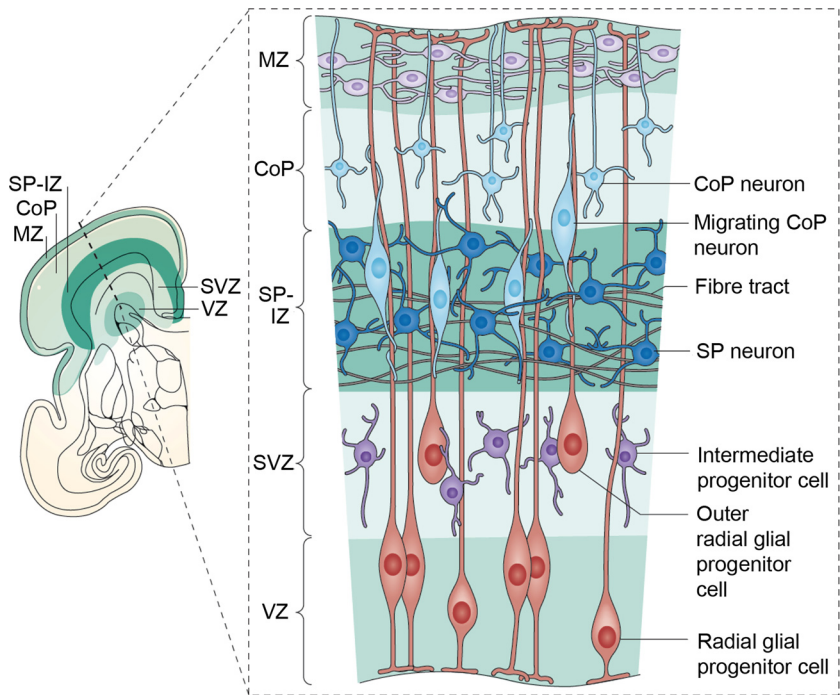
The development of the human brain spans many years: it is first at about the age of 40 years that the nervous system obtains its full-blown adult configuration (De Graaf-Peters and Hadders-Algra, 2006). The developmental processes are the result of a continuous interaction between genes and environment, activity and experience (Ben-Ari and Spitzer, 2010; Spitzer, 2006). In the following two sections the developmental processes in the cerebral cortex and cerebellum are addressed. Note that prenatal ages are expressed in weeks postmenstrual age (PMA) and not in weeks post-conception. As far as possible, PMA was verified with data provided on fetal crown-rump length.

**3.1.1.1. Developmental processes in the cerebral cortex.** Neural development starts in the fifth week PMA with the development of the neural tube (Nakatsu et al., 2000). Shortly after closure of the neural tube specific areas near the ventricles start to generate neurons. The majority of neurons is formed between 5 and 25–28 weeks PMA, with the first cortical neurons emerging at 6.5 weeks (Bystron et al., 2008; Kostović et al., 2015; Lui et al., 2011; Malik et al., 2013; Marín-Padilla, 2014; Zecević, 1993). They are generated in the germinal layers near the ventricles and move from their place of origin radially or tangentially to their final place of destination in the more superficially located cortical plate (human data: Bystron et al., 2008; Lui et al., 2011; Marín-Padilla, 1995; Ortega et al., 2018; mammalian data: Métin et al., 2008). The neural migration is guided by the shafts of transient radial glial cells (Fig. 3; Hoerder-Suabedissen and Molnár, 2015; Rakic, 2009). Migration peaks earlier in the occipital and temporal regions (around 20 weeks PMA) and in the parietal cortex (23 weeks PMA) than in the frontal cortex (26 weeks; Trivedi et al., 2009). Thereafter migratory

activity decreases so that around term age only few radially migrating neurons are found (Sidman and Rakic, 1973; Trivedi et al., 2009). Catts et al. (2013) suggested, however, on the basis of animal data, that tangential migration of cortical interneurons in the frontal cortex may continue during the human infant's first postnatal year. During migration neurons start to differentiate. Neuronal differentiation is a complex process that not only consists of the production of axons, dendrites, and synapses with neurotransmitters, but also of the creation of the intracellular machinery and the complex neuronal membranes.

During the early phases of cortical development focus is not on the cortical plate but on a temporary structure, the subplate (Hoerder-Suabedissen and Molnár, 2015; Judaš et al., 2013; Kostović and Rakic, 1990). The subplate is situated between the cortical plate and the intermediate zone, i.e., the future white matter (Figs. 3 and 4; Kostović and Rakic, 1990). It is a transient structure in placental mammals, most conspicuously present in the developing brain of primates, in particular in that of the human (Duque et al., 2016; Hoerder-Suabedissen and Molnár, 2015; Kerschensteiner, 2014; Molnár et al., 2006). It contains a variety of neurons, most of which are glutamatergic (Kostović et al., 2015). At the age of 9–10 weeks PMA, subplate neurons develop synaptic activity (Kostović et al., 2015; Marín-Padilla, 2014; Molliver et al., 1973; Supèr et al., 1998), that most likely directly gets involved in the modulation of early motor behavior (Bayatti et al., 2008; Hadders-Algra, 2007, 2018b; Marín-Padilla, 2014; Milh et al., 2007). The subplate is thickest between 28–34 weeks PMA, when it is about four times thicker than the cortical plate (Judaš et al., 2013; Mrzljak et al., 1988; Vasung et al., 2016), and is most prominently present in the frontal and parietal association areas (Duque et al., 2016; Kostović and Judas, 2002). The subplate is the major site of neuronal differentiation and synaptogenesis and it forms the largest travel area of migrating neurons on their way to the cortical plate. In addition, it is the chief site of synaptic activity in the midfetal brain (Kostović et al., 2015; Moore et al., 2011). The latter is reflected by the extensive dendritic arborization and widespread axonal projections of the subplate neurons (animal data: Kanold and Luhmann, 2010; human data: Mrzljak et al., 1988, 1992).

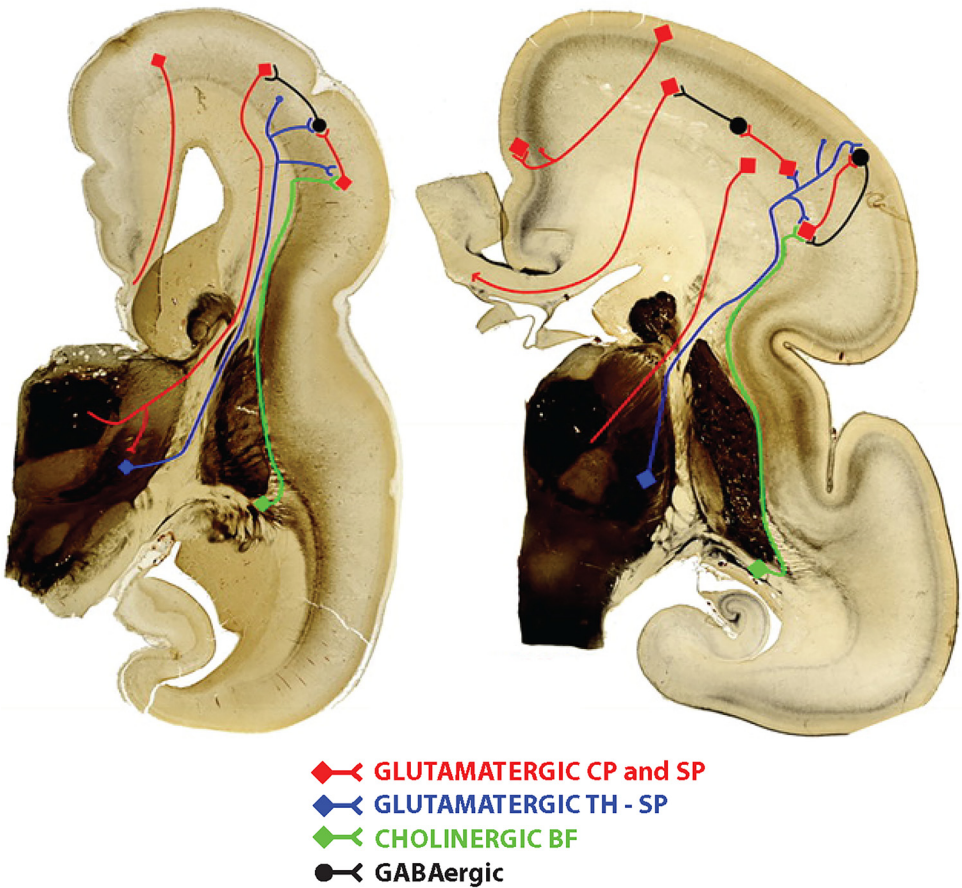
Animal experiments indicated that the spontaneously oscillating activity of the subplate neurons may play an important role in the tuning of early cortical activity (Hanganu-Opatz, 2010; Kanold and Luhmann, 2010; Luhmann et al., 2016). Kanold and Luhmann (2010) made this explicit by suggesting that the subplate neurons may act as neural amplifiers and hub neurons. The subplate also serves as a waiting and sculpturing compartment for growing cortical afferents. The earliest afferents that reach the subplate are monoaminergic fibers originating in the brain stem (around 14 weeks PMA; Kostović et al., 2015; Nobin and Björklund, 1973). Soon thereafter, at 14–16 weeks PMA, the first thalamocortical afferents arrive (Fig. 4; Krsnik et al., 2017). Ferret data indicated that these afferents allow the subplate neurons to respond to sensory stimulation (Wess et al., 2017). With increasing fetal age, the number and diversity of afferent fibers increases, including basal forebrain afferents, corticocortical afferents, and callosal afferents (Kostović et al., 2014b; Krsnik et al., 2017; Takahashi et al., 2012). The invasion of afferent fibers is so strong that it causes a wide displacement of the subplate neurons (Duque et al., 2016). Between 20–25 weeks PMA the thalamocortical and basal forebrain afferents form the major proportion of the afferents in the subplate zone (Fig. 4; Vasung et al., 2017). Thereafter, the callosal and association fibers are more prominently present (Kostović and Judas, 2002; Kostović and Jovanov-Milosević, 2006; Kostović et al., 2014b; Krsnik et al., 2017; Vasung et al., 2017). Little information is available about the efferent connections of the subplate neurons. Mrzljak et al. (1988) reported that about half of their axons followed an ascending course, the other half a descending course. Cat and ferret data indicated not only that subplate neurons project to the thalamus and the contralateral hemisphere (Antonini and Shatz, 1990), but also that the projections to the thalamus and other subcortical areas occur already at



**Fig. 3.** Schematic representation of the human cerebral cortex at 28 weeks PMA. On the left a coronal section is shown; the inset box on the right provides details of the developmental processes. The ventricular zone (VZ) and subventricular zone (SVZ) constitute the germinal matrices where cell division occurs. The first generations of cells are generated in the VZ, the later generations in the SVZ. The SVZ is a structure that expanded during phylogeny; it is especially large in primates (Ortega et al., 2018). The radial glial cells span their shafts between the germinal layers and the outer layer of the cortex (marginal zone (MZ)). The first generation neurons have migrated to the subplate (SP) – they participate in the functional fetal cortex; later generations of neurons migrate to the cortical plate (CoP). Figure reproduced from Hoerder-Suabedissen and Molnár (2015) with permission from the authors and the Nature Publishing Group.

18.5 wk

28 wk



**Fig. 4.** Two cross-sections through the fetal cortex stained with cholinesterase. The left panel shows the cortex of a fetus of 18.5 weeks PMA. It shows the emerging circuitries in the cortical subplate: the first glutamatergic thalamocortical afferents (TH-SP; blue) and cholinergic basal forebrain fibers (BF; green) contacting subplate neurons. The cross-section also illustrates the presence in the subplate of GABA-ergic (black) and glutamatergic (red) interneurons, and glutamatergic neurons with descending efferents (red). The right panel shows the cortex of a fetus of 28 weeks PMA. It illustrates the emergence of the permanent circuitries in the cortical plate, i.e., the onset of the phase in which two circuitries co-exist: the transient circuitries in the cortical subplate and the permanent circuitries in the cortical plate. The thalamocortical afferents (blue) do not only make synaptic connections with subplate neurons, but also with neurons in the cortical plate. Also GABA-ergic interneurons (black) and glutamatergic neurons (red) with descending fibres can now be found in the cortical plate. Simultaneously, complex circuitries and functionally active circuitries can be found in the subplate, including thalamocortical afferents (blue), cholinergic basal forebrain afferents (green) and GABA-ergic (black) and glutamatergic (red) interneurons. Figure by courtesy of Dr. I. Kostović, University of Zagreb. The figure has not been published previously (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

an age that is equivalent to 9–10 weeks PMA (McConnell et al., 1989; Workman et al., 2013).

When the thalamocortical afferents have arrived in the subplate, they first “wait” there for several months before they relocate - from 25 to 26 weeks PMA onwards - into their final target, the cortical plate (Fig. 4; Judaš et al., 2013; Kostović and Judas, 2007, 2010; Kostović et al., 2015; Krsnik et al., 2017). The interhemispheric callosal and intrahemispheric afferents follow; also they invade the cortical plate (Kostović and Judas, 2010). During this period of reallocation of afferent connections, the subplate gradually decreases in size as the subplate neurons undergo programmed cell death and later generated neurons start to populate the cortical plate (Judaš et al., 2013; Kostović and Rakic, 1990; Kostović et al., 2014a). Not all subplate neurons die, a proportion of these neurons survives and transforms into interstitial GABA-ergic neurons of the superficial subcortical white matter, also present in the adult brain (Judaš et al., 2013; Kostović et al., 2011).

As the cortical plate expands, the cortex increases in size and gyrification starts (Kostović and Judas, 2010) – during the second half of gestation the cortical volume increases about twentyfold (Andescavage et al., 2017). It should be realized that in the third trimester the human cortex is characterized by the co-existence of two separate but interconnected cortical circuitries: the transient fetal circuitries centered in the subplate and the immature, but progressively developing permanent circuitry centered in the cortical plate that includes the long corticocortical and interhemispheric commissural pathways (Judaš et al., 2013; Kostović et al., 2015; Takahashi et al., 2012). This means, for example, that in this period thalamocortical afferents do not only innervate subplate neurons, but also neurons in the cortical plate (Fig. 4; Krsnik et al., 2017). The duration of the ‘double circuitry’ phase differs for the various regions in the cortex. For instance, the final phase of permanent cortical circuitry is reached around 3 months post-term in the primary motor, sensory and visual cortices, but first around the age of one year in the associative prefrontal cortex (Kostović et al., 2014a, 2014b). Interestingly, those regions that develop first and are evolutionary older, such as the primary sensory areas, tend to be used in adulthood in more tasks than later developing and phylogenetically younger regions – presumably because the former have been longer around and could be integrated in more neural coalitions (Anderson and Finlay, 2014).

The gradual shift from subplate activity to cortical plate activity is most likely reflected in the neonatal electroencephalogram (EEG). From 24–26 weeks PMA spontaneous activity transients (SATs), that indicate endogenous neural activity, can be observed (Vanhatalo et al., 2005; Vanhatalo and Kaila, 2006). The SATs occur first focally and randomly in the visual, auditory and somatosensory cortices (Vanhatalo and Kaila, 2006), coincident with the ingrowth of the thalamocortical afferents in the cortical plate (Judaš et al., 2013; Kostović and Judas, 2007, 2010; Kostović et al., 2015; Krsnik et al., 2017). With increasing age, the SATs become more widespread, longer in duration and smaller in amplitude, and around term age the SATs are bilaterally synchronous and organized in frontal and parieto-occipital modules (Omidvarnia et al., 2014; Vanhatalo and Kaila, 2006). During the first months post-term the SATs gradually disappear (Vanhatalo et al., 2005). During SAT-development, also the ongoing EEG-activity changes with age, to get its full continuous characteristics around 3 months post-term (André et al., 2010; Eisermann et al., 2013; Vanhatalo and Kaila, 2006).

The following two examples show the importance of the interaction of the cortical afferents with the subplate neurons for the development of the complex network organization of the human cortex. First, animal experiments showed that ablation of the subplate prevents the specialized mapping of the visual cortex into ocular dominance columns and of the somatosensory cortex into whisker barrels (Kanold et al., 2003; Tolner et al., 2012). Second, a recent study by Duque et al. (2016) demonstrated that the size of the subplate depends on the number of afferent fibers and therefore is largest in the cortical association areas.

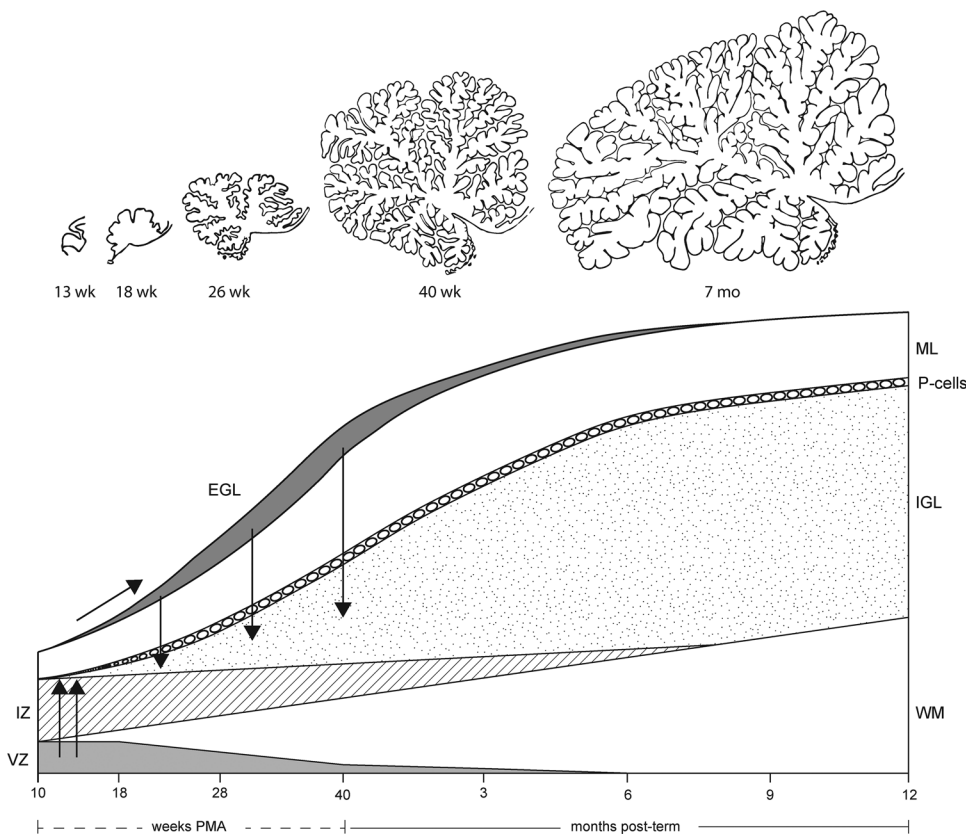
Brain development does not only imply the generation of neurons

and connections, it also involves regressive phenomena. The process of neuronal death was already mentioned above. It is assumed that in the mammalian central nervous system about half of the created neurons die off through apoptosis (Lossi and Merighi, 2003). Animal experiments indicated that apoptosis is the result of interaction between endogenously programmed processes and chemical and electrical signals induced by experience (Lossi and Merighi, 2003). In the cerebral cortex apoptosis is very active in the third trimester of gestation (Rabinowicz et al., 1996). Regressive processes do not only sculpt the neuronal population, also the number of axons and synapses is adjusted by elimination (Innocenti and Price, 2005). Well-known examples are the pruning and tuning of the corpus callosum (in the third trimester and the first two months post-term; Kostović and Jovanov-Milosević, 2006) and that of the corticospinal tract. The latter starts during the last trimester of gestation, and continuing in the first two postnatal years the initially bilateral corticospinal projections in the spinal cord are reorganized into a mainly contralateral fiber system (Eyre, 2007). This reorganization is activity driven and use dependent, as is illustrated by the effect of an early unilateral lesion of the brain. The latter results in asymmetrical activation of the spinal cord, which, in turn, induces a preferential strengthening of the activity from the ipsilateral projections from the contra-lesional hemisphere in comparison to the contralateral projections from the ipsi-lesional hemisphere (Eyre, 2007; Williams et al., 2017). It is assumed that the elimination of synapses in the brain starts during the mid-fetal period and plays a role in the reorganization of the afferent input to the cortical plate (Hoerder-Suabedissen and Molnár, 2015). Animal data indicated that especially synapses involved in weaker connections are removed (Le Bé and Markram, 2006). However, in the cerebral cortex synapse elimination is most pronounced between the onset of puberty and early adulthood (Petanjek et al., 2011).

Brain development also involves the creation of glial cells. Total final number of the glial cells matches that of the neurons (about 85 billion; Azevedo et al., 2009). Glial cell production occurs in particular in the second half of gestation (Kostović et al., 1995). It includes the generation of oligodendrocytes, cells that are involved in axonal myelination. Oligodendrocyte development peaks between 28 and 40 weeks PMA (Volpe, 2009b). Prominent myelination is present in the third trimester of gestation and the first 6 months postnatally. (Haynes et al., 2005; Yakovlev and Lecours, 1967). It should be realized, however, that myelination is a long-lasting process, that is first completed around the age of forty years (Dubois et al., 2014; Lebel et al., 2008; Yap et al., 2013; see section 3.2.1).

From early age onwards neural tissue is characterized by neurotransmitters and their receptors. Catecholamines, serotonin,  $\gamma$ -aminobutyric acid (GABA) and excitatory amino acids including glutamate have been described in the fetal cerebral cortex from 8 to 10 weeks PMA (human data: Al-Jaberi et al., 2015; Zecevic and Verney, 1995; review based on animal and human data: Herlenius and Lagercrantz, 2010). In the few weeks before and after term age the noradrenergic  $\alpha$ 2-receptors in the brain's white matter and in many brain stem nuclei are transiently overexpressed; also dopamine turnover in the striatum is high (rodent data: Sanders et al., 2005; human data: Boyson and Adams, 1997; Weickert et al., 2007; review: Herlenius and Lagercrantz, 2010). At term age serotonergic axons penetrate all cortical layers, but they rapidly decrease in density a few weeks thereafter (human data: Del Olmo et al., 1998; review based on animal and human data: Herlenius and Lagercrantz, 2001). GABA initially has an excitatory function, which changes during the third trimester into an inhibitory function (rodent and primate data: Ben-Ari, 2014; human data: Dzhalala et al., 2005). It also has been suggested that the process of birth, in particular the surge of oxytocin, may play a role in the GABA-ergic switch (Ben-Ari, 2014). Evidence suggests that the glutamatergic n-methyl-D-aspartate (NMDA) receptors in the cortex know two transient periods of overexpression that occur between 13 and 21 weeks PMA and around term age (rodent data: Benítez-Díaz et al., 2003; human





**Fig. 5.** Schematic representation of the development of the human cerebellar cortex. The lower panel depicts the migratory processes and the formation of the various layers. The upward pointing arrows denote the radial migration of the Purkinje cells (P-cells) from the ventricular zone (VZ) to the Purkinje cell layer, the right pointing arrow indicates the tangential migration of the granule precursor cells; and the downward pointing arrows reflect the radially inward migration of the granule cells from the external granular layer (EGL) to the internal granular layer (IGL). The EGL is a transient structure, most prominently present between 28 week PMA and 1–2 months post-term. The upper panel depicts the process of foliation. Figure based on [Marín-Padilla, 1985](#); [Rakic and Sidman, 1970](#), and [Ten Donkelaar and Lammens, 2009](#).

IZ = intermediate zone; ML = molecular layer (the layer where finally the parallel fibers of the granule cells meet the dendritic trees of the Purkinje cells and where stellate and basket cells reside; see [Wang and Zoghbi, 2001](#)); mo = months; PMA = postmenstrual age; wk = week; WM = white matter.

data: [Ritter et al., 2001](#); review: [Herlenius and Lagercrantz, 2010](#)).

During the first three month after term age brain volume rapidly expands from 33% to 55% of adult volume ([Holland et al., 2014](#)). At term age the growth rate of the brain is estimated as 1% per day; thereafter it gradually slows down to 0.4% per day at 3 months. The in vivo magnetic resonance spectroscopy study of [Blüml et al. \(2013\)](#) underlined that the first three post-term months of brain development are characterized by large metabolic changes.

**3.1.1.2. Developmental processes in the cerebellum.** The development of the cerebellum runs a specific time course ([Dobbing and Sands, 1973](#)). It finally results in a structure that differs considerably in composition from that of the cerebral cortex: in the human adult the cerebellum represents about 10% of brain mass (hence the Latin name meaning 'little brain'), but it contains 80% of the brain's neurons ([Azevedo et al., 2009](#)).

Cells in the cerebellum originate from two different proliferative zones ([Rakic and Sidman, 1970](#); [Volpe, 2009a](#); [Wang and Zoghbi, 2001](#)). The dorsomedial ventricular zone gives rise to the Purkinje, stellate and basket cells of the cerebellar cortex, and the cells of the deep cerebellar nuclei. Cell proliferation in the ventricular zone starts at week 10 PMA, and the Purkinje cells begin to migrate radially at 11 weeks PMA ([Fig. 5](#)). Already at week 15 PMA all Purkinje cells have been produced ([Rakic and Sidman, 1970](#)). The arrangement into the typical monolayer of Purkinje cells occurs between week 18 and 28 PMA ([Rakic and Sidman, 1970](#)). Between week 28 and week 30 PMA, the Purkinje cells get their typical appearance with an elaborate apical dendritic tree: their basal dendrites are reabsorbed, while their apical dendrites are retained ([Marín-Padilla, 1985](#)). This process of Purkinje cell transformation occurs in close interaction with the arrival of the climbing fibers, the afferents from the inferior olive. Initially the climbing fibers contact the soma of the Purkinje cells; thereafter they gradually climb the dendritic tree. The latter process continues until at least 8 month post-term ([Marín-Padilla, 1985](#)).

The other proliferative zone consists of the dorsolateral sub-ventricular zone of the rhombic lip. From 12–23 weeks PMA this zone gives rise to the granule cells, the most numerous cells of the cerebellum ([Rakic and Sidman, 1970](#); [Volpe, 2009a](#); [Wang and Zoghbi, 2001](#)). The granular precursor cells migrate tangentially over the surface of the cerebellum to form - from 13 weeks PMA onwards - the external granular layer ([Fig. 5](#)). From 15 weeks PMA the external granular layer becomes a very active proliferative zone reaching its maximum size at 28–34 weeks PMA ([Ábrahám et al., 2001](#); [Rakic and Sidman, 1970](#)). From the external granular layer the granule cells migrate radially inward, via the Bergmann radial glia, to the molecular layer and, in particular, to the internal granular layer. The latter layer grows especially between 18 weeks PMA and 3 months post-term ([Lossi et al., 1998](#); [Rakic and Sidman, 1970](#); [Ten Donkelaar and Lammens, 2009](#)). The external granular layer gradually dissolves, due to migration and apoptosis. The reduction of the external granular layer starts with a minimal decline between 34 weeks PMA and 1–2 months post-term, which is followed by a reduction of about 50% at 3–4 month post-term ([Lossi et al., 1998](#); [Rakic and Sidman, 1970](#)). It takes however until the second half year of post-term life before the external granular layer has entirely disappeared ([Ábrahám et al., 2001](#); [Rakic and Sidman, 1970](#)).

The enormous proliferative activity of the cerebellum causes a rapid increase in cerebellar volume during the second half of gestation (MRI and ultrasound studies: [Andescavage et al., 2017](#); [Chang et al., 2000](#); [Makropoulos et al., 2016](#); histological data: [Rakic and Sidman, 1970](#)). The explosive cell production also induces the formation of the cerebellar folia ([Loeser et al., 1972](#); [Rakic and Sidman, 1970](#); [Fig. 5](#)). It is estimated that during the third trimester of gestation the process of foliation causes a 30-fold increase of the cerebellar surface ([Rakic and Sidman, 1970](#); [Volpe, 2009a](#)).

Myelination in the cerebellum starts at mid-gestation ([Milosevic and Zecevic, 1998](#)). By week 28 the inferior cerebellar peduncles (with efferents to the medulla and spinal cord) and superior cerebellar peduncles (with efferents to the midbrain and thalamus) are visibly



myelinated; this is not the case for the middle cerebellar peduncles, the major afferent connections to the cerebellum (Triulzi et al., 2005). A phase of rapid myelination of the cerebellum follows between term age and 3–4 months post-term. This includes myelination of the middle cerebellar peduncles and the deep cerebellar nuclei (Triulzi et al., 2005). The net-result of the rapid myelination and the continuing cell proliferation is a doubling of cerebellar volume during the first 3 months post-term (Holland et al., 2014).

### 3.1.2. Functional connectomics

Resting state fMRI studies in fetuses and infants are highly challenging (Mongerson et al., 2017; Smyser and Neil, 2015). Nevertheless, some studies have been successful. The studies in fetuses aged 20 to 38 weeks PMA indicated that bilateral functional networks are present from 20 weeks PMA onwards (Jakab et al., 2014; Schöpf et al., 2012; Thomason et al., 2013, 2015). Highest activity is found in the cortical subplate (Schöpf et al., 2012). The strength in connectivity within the motor, visual, thalamic, frontal and parietal networks and in the sub-cortical regions (thalamus, caudate and putamen) grows with increasing fetal age (Jakab et al., 2014; Schöpf et al., 2012; Thomason et al., 2013, 2015). The increase in connectivity strength occurs especially in the short range and interhemispheric connections, and is characterized by region-specific spurts: it peaks in the occipital region at 24–25 weeks PMA, in the temporal region at 26 weeks, frontally at 26–27 weeks, and in the parietal region at 27–28 weeks PMA (Jakab et al., 2014). This may imply that the phylogenetically older regions develop faster than the younger ones (Jakab et al., 2014). Activity in the higher-order default-mode network has been demonstrated first at 36 weeks PMA (Thomason et al., 2015). The interhemispheric connectivity develops faster than the intrahemispheric connectivity; its strength also increases quicker in the medial than in the lateral cortical structures (Thomason et al., 2015).

Studies in low-risk preterm infants largely confirmed the findings of the fetal studies (Ball et al., 2014; Doria et al., 2010; Smyser et al., 2010) and showed that a ‘small world’ organization and ‘rich club’ interconnectivity of cortical hubs (see Fig. 1) are present at 30 weeks PMA (Ball et al., 2014; Cao et al., 2017). During the preterm weeks the structure of the rich clubs gradually expands (Cao et al., 2017; Van den Heuvel et al., 2015). Arichi et al. (2017) demonstrated that in preterm infants aged 32–26 weeks PMA delta brush activity (the most common SAT) in the EEG was associated with haemodynamic activity in the insular and temporal cortices (indicated by fMRI). This may suggest that the insula, which becomes an important hub in the developing cortex, is a major source of the SATs (Arichi et al., 2017; Thomason, 2018). It should be realized, however, that the studies in preterm infants also demonstrated that preterm birth affects network integrity at term age, as it is associated with alterations in cortico-subcortical and short-distance corticocortical connections, a reduced complexity in resting state activity, and absent activity in the default-mode network (Ball et al., 2014; Smyser et al., 2010, 2016).

At term age, cortical hubs are primarily found in the primary motor, somatosensory, auditory and visual cortices and to a limited extent only in the association areas (Fransson et al., 2011, 2009). This means that the cortical hubs are especially found in the areas where the permanent circuitries first reach their final layout. This organization of the hubs differs largely from that in adults in whom the cortical hubs are mainly localized in the association cortex, such as the insula region, precuneus and medial prefrontal cortex (Fransson et al., 2011).

### 3.1.3. Summary of the transient subplate phase and clinical implications

The first year after conception is characterized by high developmental activity in the brain, especially in the cortical subplate and cerebellum. The latter structures show the most dramatic changes during the second half of gestation and the first three months post-term. The transient subplate pairs a high rate of neatly orchestrated developmental changes and interactions with clear functional activity. The

subplate acts as a hub, as suggested by Kanold and Luhmann (2010), and confirmed by fMRI. This underlines its critical role in brain development.

The huge developmental activity in the brain during the second half of gestation induces a high vulnerability in infants born preterm. It is well established that prematurely born infants are at high risk of cerebral palsy, cognitive impairment and psychiatric disorders, including ASD and ADHD. The risk increases with decreasing gestational age at birth (Delobel-Ayoub et al., 2009; Johnson and Marlow, 2011; Lindström et al., 2009; Pascal et al., 2018). A minority of the preterm infants acquires a major lesion of the brain, e.g., focal or cystic periventricular leukomalacia, severe intraventricular hemorrhage with periventricular infarction, or cerebellar hemorrhage (Pierson and Al Sufiani, 2016; Volpe, 2009b). However, a large proportion of preterm infants incurs mild diffuse damage, for instance diffuse, non-cystic periventricular leukomalacia, loss of cortical and subcortical (e.g., thalamus, basal ganglia) gray matter, and loss of cerebellar volume (Penn et al., 2016; Volpe, 2009b). Important elements in the ‘encephalopathy of prematurity’ (Volpe, 2009b) – in which chronic hypoxia-ischemia acts as a major causative agent – are disrupted oligodendrocyte maturation resulting in hypomyelination and altered neuronal maturation (Back and Miller, 2014; Penn et al., 2016; Salmaso et al., 2014; Volpe, 2009b). It has been suggested that the subplate may play a crucial role in the ‘encephalopathy of prematurity’ (Penn et al., 2016; Pogledic et al., 2014). Animal experiments have shown that hypoxia-ischemia induces disruption of the dendritic arborization of the subplate neurons, and alters their synaptic activity and excitability (McClendon et al., 2017; Sheikh et al., 2018). In addition, a study in human preterm infants demonstrated that diffuse periventricular leukomalacia is associated with microglia activation in the subplate, which may interfere with the morphogenetic function of the subplate (Pogledic et al., 2014). The disturbances and altered maturation of the cerebral cortex, that are expressed by decreased volumes of grey and white matter, are often accompanied by decreased volumes of the cerebellum (Bouyssi-Kobar et al., 2016). This association may be brought about by a shared vulnerability for risk factors, but also by diaschisis, i.e., the induction of secondary damage in the cerebellum by remote primary pathology in the cerebral cortex (Limperopoulos et al., 2010, 2014; Volpe, 2009b).

The fMRI data indicated that the functional connectivity of preterm infants at term age differs from that of infants born at term. Long-term follow-up showed that the altered connectivity persists into adolescence and adulthood – even in individuals with typical function in daily life (Degnan et al., 2015a, b; White et al., 2014). Interestingly, altered connectivity, including decreased hub connectivity and altered balances between local and global connectivity, also is a consistently reported feature of resting state fMRI in individuals with neurodevelopmental disorders, such as ASD, ADHD and schizophrenia (Alaerts et al., 2015; Castellanos and Aoki, 2016; Itahashi et al., 2014, 2015; Kambeitz et al., 2016; Kennedy and Courchesne, 2008; Qiyang et al., 2017; Posner et al., 2014; Van den Heuvel et al., 2013). These neurodevelopmental psychiatric disorders share complex etiologies with a poly-genetic component and a heterogeneous profile of prenatal and perinatal risk (Birnbaum and Weinberger, 2017; Lyall et al., 2017; Thapar and Cooper, 2016). On the basis of these findings, I hypothesize that interference with the wealth of neurodevelopmental processes occurring in the second half of gestation and the first three postnatal months, in particular interference with the developmental activity in the subplate and its associated secondary effects, may be an important pathogenetic mechanism in the development of ASD, ADHD and schizophrenia. The concept that the developmental disruption of subplate maturation plays a pivotal role in ASD and schizophrenia is supported by increasing neuropathological evidence of supernumerary interstitial cells in the superficial gyral white matter of individuals with these disorders (Akbarian et al., 1993; Eastwood and Harrison, 2005; Hutsler and Casanova, 2016; Kostović et al., 2011). Similar human evidence is

not available in ADHD, possibly due to the heterogeneous and multi-causal pathway of ADHD in which environmental factors act as a major modifier of symptomatology (Batstra et al., 2014; Choi et al., 2017; Thapar and Cooper, 2016). However, rodent data suggest that in a subpopulation of individuals with ADHD developmental disruption of subplate maturation may play a role (Berkowicz et al., 2016).

### 3.2. After 3 months post-term: focus on ontogeny of the permanent circuitries

#### 3.2.1. Structural development

In the first postnatal year, the volume and the surface of the neocortical grey and the volume of the subcortical grey nearly doubles (Gilmore et al., 2012; Li et al., 2013; Poh et al., 2015). In the second postnatal year, the expansion of these structures continues, but more slowly. Also the focus of expansion changes, it moves from the primary sensory areas to the association areas in the parietal, frontal and temporal lobes. This means that the association areas especially expand when they have obtained their permanent circuitries after subplate dissolution. The increases in cortical grey are paralleled by processes of dendritic growth of the cortical pyramidal neurons (Petanjek et al., 2008). Also white matter develops rapidly during the first two postnatal years. Notwithstanding substantial regional and inter-individual variation it is possible to distinguish in this white matter development distinct patterns: proximal pathways myelinate before distal ones, sensory fibers before motor ones and projection fibers before association pathways (Brody et al., 1987; Dubois et al., 2013, 2014; Haynes et al., 2005; Kinney et al., 1988; Yakovlev and Lecours, 1967).

After the age of 2 years brain development continues, but at a slower pace. Total brain volume – that is highly variable in typically developing children – only changes to a minor extent with increasing age. It shows a minimal peak around the age of 12 years (Brain Development Cooperative Group, 2012; Giedd et al., 1999; Lenroot and Giedd, 2006). The minor changes in total brain volume are the net result of changes in grey and white matter: grey matter volume gradually decreases and white matter volume increases with increasing age (Brain Development Cooperative Group, 2012; Giedd et al., 1999; Østby et al., 2009; Sowell et al., 2004). The decreases in grey matter vary across region; they are most pronounced in the parietal and occipital regions. The increases in white matter are however rather uniform throughout the cortex (Brain Development Cooperative Group, 2012). Also the corpus callosum increases gradually with increasing age; at preschool age the focus of growth is in the frontal parts, during school age and adolescence this focus shifts to the caudal parts, i.e., the parts connecting the temporal and parietal cortices (Thompson et al., 2000; Toga et al., 2006). The major processes underlying the changes in grey matter are the reconfigurations of the dendritic arbors occurring in particular during preschool age (Koenderink and Uylings, 1995; Petanjek et al., 2008) and the lifelong synaptic reorganization, i.e., the net result of synapse formation and synapse elimination (Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011; Purves, 1994). The changes in white matter are largely based on myelination, a process that continues until the age of 40 years when the last intracortical, in particular the long fronto-temporal connections such as the cingulum, and the short connections in the superficial cortical white matter, complete myelination (Dubois et al., 2014; Lebel et al., 2008; Ouyang et al., 2017; Yap et al., 2013).

#### 3.2.2. Functional connectomics

Resting state fMRI studies have been performed mainly in neonates and children aged 1 and 2 years. The studies did not address changes around 3 months post-term. The studies available indicated that in the first two postnatal years local connectivity decreases and global connectivity via long-range functional connections increases in a process especially characterized by a complex reorganization of the hubs (Damaraju et al., 2014; Fan et al., 2011; Gao et al., 2016; Hagmann

et al., 2010; Yap et al., 2011). In the first year developmental progress in the motor and somatosensory networks surpasses that in the visual networks; at the age of two years the difference in connectivity between sensorimotor and visual networks has disappeared (Gao et al., 2016; Lin et al., 2008). Of the higher order networks, the default-mode network is the first to develop. From its primordial presence at term age it develops into a network connecting the hippocampus and parahippocampus, the inferior parietal cortex and the posterior cingulate cortex at the age of 6 months. Thereafter, in the following six months, the medial prefrontal cortex and lateral temporal cortex are integrated (Gao et al., 2009, 2015, 2016). Functional connectivity between thalamus and sensorimotor cortex and thalamus and typical salience network regions, i.e., insula, anterior cingulate and prefrontal regions, has been demonstrated from term age onwards. Interestingly, the integrity of the thalamo-salience networks connectivity at 1 year of age has been associated with memory function at 2 years (Alcauter et al., 2014). Functional connectivity between the thalamus and the default-mode network first develops in the second postnatal year (Alcauter et al., 2014).

No resting state fMRI data in preschool age children are available. Between school age and adulthood the developmental shift from less local connectivity to more global connectivity gradually continues (Fair et al., 2007, 2009; Khundrakpam et al., 2013; Stevens et al., 2009; Supekar et al., 2009) and the default-mode network slowly obtains its adult characteristics (Fair et al., 2008). Between childhood and adolescence the connectivity between frontal hubs and cortical and non-cortical non-hub regions increases. Between adolescence and adulthood the connectivity between cerebellar hubs and cortical non-hub regions increases (Hwang et al., 2013).

#### 3.2.3. Summary of the developmental processes after the age of 3 months and clinical implications

After 3 months post-term the brain's grey and white matter continue to increase. The grey matter in the association areas expands especially after the age of 1 year, i.e., when the subplate has dissolved. Also white matter growth takes longest time in the association areas. After the age of two years, grey matter gradually decreases, whereas white matter shows a protracted course of increase. These changes are paralleled by gradual developments in the focus of connectivity, which moves from local to global.

The protracted course of brain development is paralleled by developmental changes in motor, cognitive and behavioral function continuing at least until early adult age: the infant, who is totally dependent on caregiver support, changes into the adult, who independently organizes her/his life. The lengthy neuromaturation explains why it takes developmental time before neurodevelopmental disorders become clinically manifest. For instance, cerebral palsy, that is mostly caused by a marked lesion of the cerebral white and/or gray matter (Korzeniewski et al., 2008), is generally first diagnosed from about the end of the first postnatal year onwards, whereas in some children it may take several years before the clinical picture is established (Granild-Jensen et al., 2015; Smithers-Sheedy et al., 2014). The timing of the manifestation of the clinical signs of cerebral palsy most likely is related to developmental changes in the corticospinal tract (Clowry, 2007; Eyre et al., 2007). The clinical signs of ASD and ADHD generally emerge during preschool age (Johnson et al., 2015; Kaplan and Adelman, 2011; Zwaigenbaum and Penner, 2018); those of schizophrenia mostly during adolescence and young adulthood (Van Os and Kapur, 2009; Sawa and Snyder, 2002). The difference in the age of onset of symptomatology between the neuropsychiatric disorders suggests a difference in the timing of the onset of atypical neurodevelopment, or - if we follow the idea of a crucial role of the subplate in developmental neuropsychiatric disorders – a difference in the timing of the developmental disruption of the subplate. As ADHD and ASD are clearly associated with preterm birth (Delobel-Ayoub et al., 2009; Johnson and Marlow, 2011), it may be surmised that the window of highest vulnerability for the developmental disruption of the subplate in these disorders is the last trimester

before term age. Schizophrenia is associated with a variety of prenatal, perinatal and early childhood factors (Brown, 2011; Van Os and Kapur, 2009). This finding, in combination with schizophrenia's altered connectivity in the association cortices, may suggest that schizophrenia's window of highest vulnerability ranges from mid-gestation to the end of the first post-natal year – corresponding to the subplate presence in these areas. The idea is that developmental disruption of the subplate acts as a primary disorganizer of subsequent developmental processes, in particular of the development of the cortical plate and its local and global connectivity. Genetic factors may act as facilitators of, or protectors against the subplate's vulnerability and the cascading effects of its developmental disruption.

#### 4. Concluding remarks

The development of the human brain is a long-lasting intricate process of epigenetic cascades that mediate the ongoing interaction between genetic information, spontaneous activity and environmental information. The developmental changes in the brain happen especially during the prenatal period and in the first two postnatal years. Yet, the most significant changes occur during the second half of gestation and the first three months post-term in the cortical subplate and cerebellum. The transient subplate pairs a high rate of complex developmental changes and interactions with clear functional activity. It also mediates fetal and young infant behavior, that is characterized by variation and exploration (Hadders-Algra, 2018a). The reviewed literature suggests that disruption of subplate development plays a pivotal role in developmental disorders, such as cerebral palsy, ASD, ADHD and schizophrenia, where type and timing of developmental disruption may determine the nature of the outcome. Large focal lesions, involving also the periventricular white matter may result in cerebral palsy, diffuse interference with subplate development rather in ASD, ADHD and schizophrenia. Putatively the window of highest vulnerability to develop ASD and ADHD is narrower – with a focus in the last trimester before term age – than that associated with schizophrenia, where the window may range from the second half of gestation to the end of the first postnatal year.

The dissolution of the subplate, which gives way to the establishment of the permanent circuitries in the cortical plate, occurs around 3 months post-term in the primary sensory and motor cortices, and around 1 year in the phylogenetically relatively young frontal, temporal and parietal association areas. The data reviewed above indicate that these developmental changes are paralleled by a gradual shift from dominant hub activity in the primary sensory and motor areas to distributed activity in multiple networks, including the higher order default-mode network. After the age of one year developmental changes consist of continuous reconfigurations of network activity, with a gradual decrease of local connectivity in favour of an increase in global, long-range connectivity.

The disappearance of the subplate in the primary sensory and motor areas at 3 months post-term coincides with a major transition in motor behaviour: the spontaneously generated general movements are replaced by goal directed movements, such as mutual manipulation of fingers and reaching movements, and the infant is able to properly balance the head on the trunk when held in a sitting position (Hadders-Algra, 2018a, 2018b; Prechtl, 1984). The transition around 3 months is also the age when the varied motor behavior of the infant changes from being mainly used in exploration without adaptation, to the long-lasting phase during which trial and error exploration gradually results in adaptive behaviour in many situations (Hadders-Algra, 2018a). The protracted changes in network connectivity are also accompanied by tremendous increases in cognitive and social development (e.g., Meltzoff et al., 2009; Newcombe et al., 2013; Rakison and Lawson, 2013). In addition, the long-lasting changes explain why it takes developmental time before the signs of neurodevelopmental disorders manifest themselves.

Our knowledge on the precise role of the subplate in human brain development is limited, and our understanding of the potential role of developmental disruption of the subplate is even more restricted. Future research may address these issues by combining developmental studies in animals and humans. The animal experiments allow for the elucidation of neuropathological mechanisms involved in and resulting from deviancies in subplate development. Studies in children preferably use a longitudinal design and combine multiple techniques, including resting state fMRI or multichannel EEG and clinical tools that evaluate the child's motor, cognitive and behavioral function.

#### Declaration of interest

None.

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